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Study unveils insight into a debilitating brain disease

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From the neurons that enable thought to the keratinocytes that make toenails grow–a complex canopy of sugar molecules, commonly known as glycans, envelop every living cell in the human body.

These complex carbohydrate chains perform a host of vital functions, providing the necessary machinery for cells to communicate, replicate and survive. It stands to reason, then, that when something goes wrong with a person's glycans, something goes wrong with them.

Now, researchers at the University of Georgia are learning how changes in normal glycan behavior are related to a rare but fatal lysosomal disease known as Niemann-Pick type C (NPC), a genetic disorder that prevents the body from metabolizing cholesterol properly. The findings were published recently in the *PNAS* Early Edition.

"We are learning that the problems associated with cholesterol trafficking in the cell lead to problems with glycans on the cell's surface, and that causes a multitude of negative effects," said Geert-Jan Boons, professor of chemistry in the Franklin College of Arts and Sciences and researcher at UGA's Complex Carbohydrate Research Center. "Now, for the first time, we can see what these problems are, which we hope will lead to a new understanding of diseases like NPC."

Because NPC patients are unable to metabolize cholesterol, the waxy substance begins to accumulate in the brain. This can lead to a host of serious problems, including neurodegeneration, which the researchers

hypothesize may be caused by improper recycling of glycans on the surface of an NPC patient's cells.

Glycans normally undergo a kind of recycling process when they enter the cell only to be returned to the surface recharged and ready to work. The researchers discovered that glycans in NPC cells do not do this.

"One of the secondary effects of NPC is the disruption of traffic pathways within the cell, and this can lead to altered recycling of glycans," said Richard Steet, associate professor of biochemistry and molecular biology and CCRC researcher. "The glycans come into the cell, but they won't recycle back up to the cell's surface where they must exist to function as receptors or ion channels."

"Basically, the machinery gets clogged up," Boons said.

Like downed phone lines and flooded roads in a thunderstorm, glycans get stuck inside the cell making communication and travel for these cells difficult or impossible. Without these basic abilities, the body's motor, sensory and cognitive functions begin to suffer. This might explain why NPC patients suffer from such a wide variety of neurological and psychiatric disorders, such as uncoordinated limb movements, slurred speech, epilepsy, paralysis, psychosis, dementia and hallucinations.

The researchers made these observations in fibroblasts taken from diseased patients. These cells are most commonly found in connective tissues, and they play a vital role in wound healing. However, they hope to continue their investigation into the effects of NPC by studying glycan behavior in neural cells, which make up the human brain.

While they caution that much more work must be done, they hope that an improved understanding of the roles that glycans play in neural cells will lead to new therapeutics for NPC and other diseases like it.

"It is exciting to work on projects like these, because we believe glycobiology is the next frontier, the next level of complexity," Boons said. "The time is right for new discovery."

Provided by University of Georgia